Microrheology, Stress Fluctuations, and Active Behavior of Living Cells

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We report the first measurements of the intrinsic strain fluctuations of living cells using a recently developed tracer correlation technique along with a theoretical framework for interpreting such data in heterogeneous media with nonthermal driving. The fluctuations' spatial and temporal correlations indicate that the cytoskeleton can be treated as a course-grained continuum with power-law rheology, driven by a spatially random stress tensor field. Combined with recent cell rheology results, our data imply that intracellular stress fluctuations have a nearly $1/\omega^2$ power spectrum, as expected for a continuum with a slowly evolving internal prestress.

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An accurate physical picture of the viscoelasticity and motion of the cytoskeleton is crucial for a complete understanding of processes such as intracellular transport [1], cell crawling [2], and mechanochemical transduction [2]. Microrheology [3], based on the analysis of embedded tracer particle motion, has recently emerged as an experimental probe of cytoskeleton viscoelasticity and dynamics [4–7]. The viscoelastic properties of eucaryotic cells arise from an intricate network of protein filaments driven by specialized motor proteins and directional polymerization that convert the chemical energy of adenosine triphosphate to mechanical work and motion. A cell is thus a nonequilibrium soft material whose fluctuations are actively driven. Unlike the thermal fluctuations in an equilibrium material, the amplitude and spatial distribution of active fluctuations can be controlled via biochemical signaling pathways, perhaps allowing the cell to locally adjust its mechanical properties to suit its needs. Indeed, microscopic force generators play a central role in existing cell mechanics models such as the sol-gel [8], soft glassy rheology [4], and tensegrity [9] hypotheses.

In this Letter, we extend a recently introduced method, termed two-point microrheology [10], and show that it can be used to characterize the activity of intracellular force generators by directly measuring a cell's intrinsic, random stress fluctuations. Our experimental data and theoretical framework show that a cell can be modeled as a coarse-grained viscoelastic continuum driven by a spatially random stress field having a $1/\omega^2$ power spectrum in our observable frequency range, $1 < \omega < 60$ rad/s.

There are two distinct approaches to microrheology: the active approach measures the displacements of tracer particles induced by external forces and the passive approach measures fluctuations of particle positions in the absence of driving forces. The active approach provides a direct measure of the complex shear modulus $\mu(\omega)$. In equilibrium systems the passive approach also measures $\mu(\omega)$ because of the fluctuation-dissipation theorem (FDT) [11]. Literature results in cells using single-particle versions of the two approaches yield shear moduli differing by orders of magnitude and exhibiting qualitatively different frequency dependencies [4–6]. These results are further limited by ambiguities associated with tracer boundary conditions, medium heterogeneity, and, more importantly, the applicability of the FDT. We show theoretically that data from passive two-point microrheology and active response experiments can be combined to measure the activity of molecular motors—specifically, the power spectrum of intracellular stress fluctuations—despite the cell's heterogeneity. We will first discuss current microrheology approaches and our measurements.

Microrheology relies on the Langevin equation [11] for the velocity $\mathbf{v}$ of a tracer particle,

$$m\partial_t \mathbf{v}(t) = -\int_{-\infty}^{t} dt' \gamma(t-t')\mathbf{v}(t') + \mathbf{f}_E(t) + \mathbf{f}_R(t), \quad (1)$$

where m is the mass of the tracer particle, $\mathbf{f}_E(t)$ is the external force, and $\mathbf{f}_R(t)$ is the random force arising from the medium. Stokes law states that $\gamma(\omega) = 6\pi a\mu(\omega)/(-i\omega)$ [12] for spherical tracers with radius a and no-slip boundary conditions in an isotropic, homogeneous viscoelastic medium with a complex shear modulus $\mu(\omega)$. In the active scheme, $\mathbf{f}_R(t)$ can be set to zero, and the displacement is $\mathbf{r}(\omega) = \chi(\omega)\mathbf{f}_E(\omega)$, where $\chi(\omega) = \{-i\omega[-im\omega + \gamma(\omega)]\}^{-1}$ is the response function.

Several measurements of $\chi(\omega)$ to extract the elastic moduli of the cytoskeleton of living cells have been performed [4,5]. In particular, Fabry *et al.* [4] have reported accurate measurements of the linear response to an applied torque of a few-micron-diameter magnetic bead attached to the outside of a cell and strongly coupled to the cytoskeletal network via the cell's integrin receptors. Remarkably, they found that over five decades in frequency, from 10^{-2} to 10^3 Hz, the shear modulus of several cell types was of order 1 kPa with a power-law form $|\mu(\omega)| \sim \omega^\beta$ with $0.10 < \beta < 0.30$.

Passive "one-point" microrheology is based on the correlation function $C_{r_i r_j}(t) = \langle r_i(t) r_j(0) \rangle$. In thermal equilibrium, this correlation function is related through the FDT to the response function $\chi(\omega)$:

$$C_{r_i r_j}(\omega) = \delta_{ij} \frac{2k_B T}{\omega} \mathrm{Im}\chi(\omega) \approx \delta_{ij} \frac{k_B T}{3\pi a} \frac{\mu''(\omega)}{\omega |\mu(\omega)|^2}. \quad (2)$$

The final form is valid in the window $\omega_a < \omega < \omega_b$, with the lower frequency $\omega_a \sim 10^{-2}$ Hz set by the compressional mode of the network and upper frequency $\omega_b \sim 10^5$ Hz by inertial effects [13]. Experiments typically measure tracers' mean-squared displacement (MSD), $\langle \Delta \mathbf{r}^2(\tau) \rangle = \langle \Delta r_i(t, \tau) \Delta r_i(t, \tau) \rangle$, where $\Delta r_i(t, \tau) = r_i(t + \tau) - r_i(t)$ and the brackets represent time and ensemble averages. $\langle \Delta \mathbf{r}^2(\tau) \rangle$ is related to the correlation function by $\langle \Delta \mathbf{r}^2(\tau) \rangle = \int \frac{d\omega}{2\pi} (1 - e^{-i\omega\tau}) C_{r_i r_i}(\omega)$.

Two-point passive microrheology experiments measure a two-particle displacement tensor $D_{ij}(R, \tau) \equiv \langle \Delta r_i^{(1)}(t, \tau) \Delta r_j^{(2)}(t, \tau) \rangle$, where the superscripts identify the two different tracers, the brackets represent an ensemble average over all tracer pairs and time, and R is the separation between the two tracers. In thermal systems, $D_{ij}(R, \tau)$ can be related via the FDT to the shear moduli by two-particle equivalents of $C_{r_i r_j}(\omega)$, but with the $1/a$ scaling replaced by $1/R$ scaling. Importantly, it has been shown [13,14] that $D_{ij}(R, \tau)$ is independent of tracer size, shape, and boundary conditions (to leading order in $1/R$). In cells, this allows the use of endogenous particles, unlike existing methods that attach or inject synthetic tracers which may perturb the cell. In systems where Eq. (2) is valid, $D_{ij}(R, \tau)$ and $\langle \Delta \mathbf{r}^2(\tau) \rangle$ have the same functional form vs τ, differing only by a geometrical constant. This leads to the definition of a two-point MSD, which may be considered that of an ideal Stokes particle advected by random fluctuations of the medium: $\langle \Delta \mathbf{r}^2(\tau) \rangle_2 \equiv (2R/a) D_{rr}(R, \tau)$, where D_{rr} is the tensor component of D_{ij} parallel to $\hat{\boldsymbol{R}}$.

We made passive microrheology measurements on two cultured cell lines for which shear moduli $\mu(\omega)$ had been measured previously [4]. All cells were cultured in Delbeco's Modified Eagle Medium supplemented with 10% calf serum and 5 μm/ml gentamicin in 5% CO_2. F9 cells were cultured in gelatin-coated tissue-culture flasks. Cells were passed into glass-bottom cell-culture dishes with collagen-coated coverslips and allowed to incubate for either 4–6 h (F9) or overnight (J774A.1) prior to experiments. For tracers, we visualized endogenous refractive particles in the cells using differential interference contrast microscopy and computed one- and two-particle correlations from the same multiparticle video tracking trajectories [15]. As our analysis assumes a three-dimensional continuum, we excluded trajectories from the thin lamellar region of the cell and the mechanically distinct nucleus, focusing instead on the midplane of the 6–8 μm thick cells. We typically observed ~100 submicron tracers (presumed by morphology to be lipid granules and mitochondria) within our 1 μm focal depth. Thirty minutes of data yielded $\sim 10^7$ tracer positions per cell, with respective time and space resolution of 1/60 sec and 20 nm.

Typical MSD data for cells are presented in Fig. 1. Although visual examination of the images occasionally shows ballistic tracer motion (trafficking), driven presumably by kinesin and dynein motor proteins along microtubules, the ensemble averaged $\langle \Delta \mathbf{r}^2(\tau) \rangle$ is dominated by random, apparently diffusive motion. From the two-point data, we first verified that $D_{rr} \sim 1/R$ [Fig. 1 (inset)] in the accessible range $2 < R < 8$ μm, comparable to results in other studies [9,16]. In thermal systems at least, this finding suggests that the medium may be treated as a coarse-grained homogeneous continuum on the scale R. Strikingly, the two-point displacements of intracellular tracers exhibit a superdiffusive behavior: $\langle \Delta \mathbf{r}^2(\tau) \rangle_2 \sim \tau^\alpha$ with exponent $1.30 < \alpha < 1.60$. If a living cell were an equilibrium viscoelastic medium with $\mu(\omega) \sim \omega^\beta$ as reported in Ref. [4], Eq. (2) would imply that $\langle \Delta \mathbf{r}^2(t) \rangle \sim t^\beta$. Our data show that $\alpha > \beta$ and, thus, the FDT breaks down. While the one-point MSD suggests that the motion of single endogenous tracers is dominated by diffusive motion relative to the network, which may be thermal or nonthermal in origin, recent experiments have shown $\langle \Delta \mathbf{r}^2(\tau) \rangle \sim \tau^{1.5}$ for large (several μm) phagocytosed tracers [6]. Such one particle measurements, however, cannot distinguish between advection by a driven continuum or trafficking relative to a stationary network. In contrast, our two-point MSD results unambiguously indicate that the cytoskeleton itself has large strain fluctuations driven by nonthermal forces.

In living cells, active motors not only modify the viscoelastic response of the cytoplasm, they also give rise to random, nonthermal stress fluctuations that cause

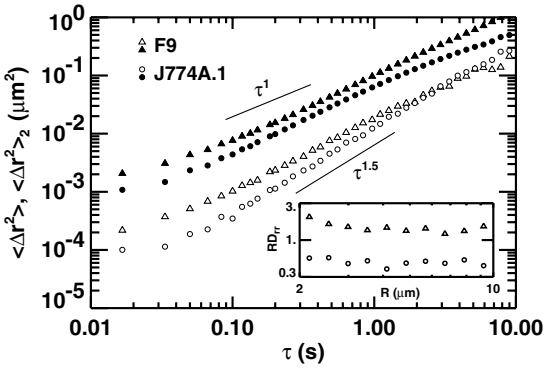

FIG. 1. One-particle (solid symbols) and two-particle (open symbols) displacements vs lag time τ for endogenous tracers in two types of cultured cells, J774A.1 mouse macrophage and F9 mouse carcinoma. Superdiffusive behavior, exponent greater than 1, indicates the effect of nonthermal fluctuations. Inset: $RD_{rr}(R, \tau = 0.067$ sec) in units of 10^{-4} μm^3 is nearly constant in both cell types, as expected for a coarse-grained isotropic continuum.

tracer particles to be subjected to random nonthermal forces. In such a system, Eq. (2) must be modified. We will outline a careful derivation below, but we can easily guess it as follows: In thermal systems, the stress tensor has a random component $s_{ij}(\mathbf{x}, t)$ whose local fluctuations are described by

$$\langle s_{ij}(\mathbf{x}, \omega) s_{kl}(\mathbf{x}', \omega') \rangle = 2\pi\Delta(\omega)\delta(\omega + \omega')\delta^3(\mathbf{x} - \mathbf{x}') \times [\delta_{ik}\delta_{jl} + \delta_{il}\delta_{jk} - \tfrac{2}{3}\delta_{ij}\delta_{kl}], \quad (3)$$

where $\Delta(\omega) = 2k_B T\mu''(\omega)/\omega$ as dictated by FDT [17]. In nonequilibrium systems, there are stress fluctuations of the same form, but with $\Delta(\omega)$ not locked to $\mu''(\omega)$, and we expect

$$C_{r_i r_j}(\omega) \approx \delta_{ij} \frac{\Delta(\omega)}{6\pi a|\mu(\omega)|^2}, \quad (4)$$

where $\Delta(\omega)$ is now interpreted as the power spectrum of the stress fluctuations whose microscopic origin is the activity of the motors. Equation (4) suggests that (i) tracers can exhibit superdiffusive behavior provided $\Delta(\omega)$ diverges sufficiently at small ω, and (ii) if an independent measure of $\mu(\omega)$ exists, then $\Delta(\omega)$ can be sensibly extracted from passive correlations data.

To avoid artifacts associated with medium heterogeneity and non-Stokes's boundary conditions, we used Eq. (6) below, which is the two-point equivalent of Eq. (4), along with rheological data reported in Ref. [4], to convert our two-point data for both cell types to $\Delta(\omega)$ as shown in Fig. 2. We found a nearly $1/\omega^2$ spectra. These typical results were replicated on 8 cells of each type. The variations of α and the power spectrum exponent among cells of each type, and within different regions of a single cell, were comparable within our measurement error. A $1/\omega^2$ spectrum corresponds to a linear decay in time of a stress-stress correlation function within our experimental time window, and would be a natural consequence of slow evolution of intracellular stress [18]. Note also that $\Delta(\omega)$ is a few orders of magnitude greater than the thermal

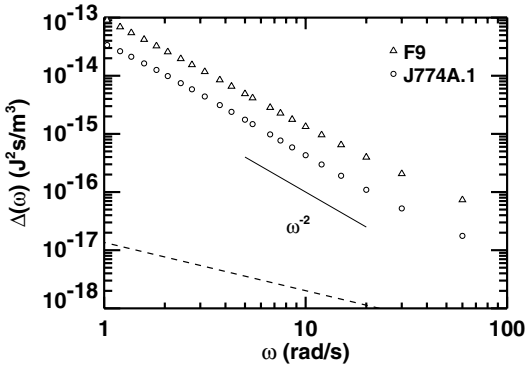

FIG. 2. The intracellular stress fluctuation spectrum $\Delta(\omega)$ as measured in two-point microrheology. The cell lines are J774A.1 macrophage and F9 carcinoma. The dashed line represents the thermal spectrum, $2k_B T\mu''(\omega)/\omega$, where $\mu(\omega)$ is measured in Ref. [4].

spectrum (dashed line), affirming that these fluctuations are driven by a nonthermal mechanism.

In the case that the shear modulus and the stress spectrum have power-law forms, our result can be simply stated. In living cells, with "power-law" modulus $\mu(\omega) \sim \omega^\beta$ and a $\Delta(\omega) \sim \omega^{-\gamma}$ spectrum, Eq. (4) implies that $\langle \Delta\mathbf{r}^2(\tau) \rangle \sim \tau^{\gamma+2\beta-1}$. If the $1/\omega^2$ spectrum we observe is universal, then one can measure the rheology exponent β via passive two-point measurements, using the formula $\langle \Delta\mathbf{r}^2(\tau) \rangle_2 \sim \tau^{1+2\beta}$. The correspondence of our explicitly intracellular results with those of Fabry *et al.* [4] supports their assertion that their measurements probe intracellular viscoelasticity as opposed to the response of a thin cortical shell.

Now, we turn to our theoretical task and address the fundamental question: Given that living cells are highly heterogeneous nonequilibrium systems in which the FDT does not apply, do two-point passive microrheological experiments overcome ambiguities associated with tracer boundary conditions and medium heterogeneity and, in conjunction with response measurements, extract the power spectrum of the continuum stress fluctuations? We first postulate that a living cell at large length scale effectively is an incompressible, viscoelastic medium characterized by a displacement field $\mathbf{u}(\mathbf{x}, t)$, whose equation of motion is given by

$$\rho \frac{\partial^2 u_i}{\partial t^2} = \partial_j \sigma_{ij}(\mathbf{x}, t) + f_i(\mathbf{x}, t), \quad (5)$$

where ρ is the coarse-grained mass density, $f_i(\mathbf{x}, t)$ is the nonthermal random force density arising from the motors, and $\sigma_{ij}(\mathbf{x}, t)$ is the stress tensor. Within linear response theory, the stress $\sigma_{ij}(\mathbf{x}, t)$ is related to the strain by $\sigma_{ij}(\mathbf{x}, \omega) = 2\mu(\omega)u_{ij}(\mathbf{x}, \omega)$, where $u_{ij} = (\partial_j u_i + \partial_i u_j)/2$ is the strain tensor and $\mu(\omega)$ the frequency-dependent shear modulus. Since there should be no net external force in a stationary cell, the random force must take the form $f_i(\mathbf{x}, t) = \partial_j s_{ij}(\mathbf{x}, t)$, where $s_{ij}(\mathbf{x}, t)$ is a random stress tensor. We assume that its average is zero and the variance is given by Eq. (3). To relate to our microrheology experiments, we relate one- and two-particle correlation functions to stress fluctuations $\Delta(\omega)$ and respond to external forces $\mu(\omega)$ as follows.

We consider two tracer particles of radius a placed in this random medium and ask the following: What forces are exerted on each particle? For simplicity, we assume that the heterogeneities near the vicinity of the tracers are well reflected by a local effective shear modulus $\mu^*(\omega)$ which may be different from $\mu(\omega)$ in the bulk. Let particle 1 (2) at $\mathbf{x}$ ($\mathbf{x}'$) undergo a displacement $\varepsilon_i^{(1)}(\omega)$ ($\varepsilon_i^{(2)}(\omega)$). First, we decompose $\mathbf{u}(\mathbf{x}, t)$ into an average part and a fluctuating part, $\mathbf{u}(\mathbf{x}, t) = \bar{\mathbf{u}}(\mathbf{x}, t) + \tilde{\mathbf{u}}(\mathbf{x}, t)$, and solve Eq. (5) subject to boundary conditions, $\bar{\mathbf{u}}_i(|\mathbf{x}| = a, \omega) = \varepsilon_i^{(n)}(\omega)$ and $\tilde{\mathbf{u}}_i(|\mathbf{x}| = a, \omega) = 0$, on the surface of the nth particle and $\bar{\mathbf{u}}_i(|\mathbf{x}|, \omega)$, $\tilde{\mathbf{u}}_i(|\mathbf{x}|, \omega) \to 0$, far away from the particles. The total force exerted by the medium on each particle has two components: an

average, $\bar{F}_i^{(n)}(\omega) = \int_{S_n} dS\hat{n}_j\bar{\sigma}_{ij}(\mathbf{x}, \omega)$, and a random part, $\tilde{F}_i^{(n)}(\omega) = \int_{S_n} dS\hat{n}_j\tilde{\sigma}_{ij}(\mathbf{x}, \omega)$, where $\bar{\sigma}_{ij} = 2\mu(\omega)\bar{u}_{ij}$ and $\tilde{\sigma}_{ij} = 2\mu(\omega)\tilde{u}_{ij}$ are, respectively, the average and fluctuating stresses, and $\hat{n}_j$ is the unit surface normal pointing towards the center of each particle. It is straightforward to compute $\bar{F}_i^{(n)}(\omega) = \sum_m \chi_{ij}^{-1\,(m,n)}(\omega)\varepsilon_i^{(m)}(\omega)$, where $\chi_{ij}^{(n,m)}(\omega)$ is the two-particle response matrix given by $\chi_{ij}^{(1,1)}(\omega) = \frac{\delta_{ij}}{6\pi a\mu^*(\omega)}$ and $\chi_{ij}^{(1,2)}(\omega) = \frac{\hat{R}_i\hat{R}_j}{4\pi R\mu(\omega)} + \frac{\delta_{ij}-\hat{R}_i\hat{R}_j}{8\pi R\mu(\omega)}$, to the lowest order in $1/R$, where $R \equiv |\mathbf{x} - \mathbf{x}'|$, the distance between the two particles and $\hat{\mathbf{R}} \equiv \mathbf{R}/R$; the noise correlators are given by $\langle\tilde{F}_i^{(n)}(\omega)\tilde{F}_j^{(m)}(-\omega)\rangle = \Delta(\omega)\chi_{ij}^{-1(n,m)}(-\omega)/\mu(-\omega)$ [19]. These results imply that $\langle\varepsilon_i^{(1)}(\omega)\varepsilon_j^{(1)}(-\omega)\rangle$ depends in a complicated way on $\mu^*(\omega)$ and $\mu(\omega)$. In contrast, the cross-correlation function as measured by two-point microrheology is

$$D_{rr}(R, \omega) \equiv \langle\varepsilon_i^{(1)}(\omega)\varepsilon_i^{(2)}(-\omega)\rangle = \frac{\Delta(\omega)}{6\pi R\,|\mu(\omega)|^2}, \quad (6)$$

to the lowest order in $1/R$, which depends only on $\mu(\omega)$ and $\Delta(\omega)$ in the bulk, and is independent of the tracers' size, shape, or boundary conditions. Thus, apart from a geometrical factor, Eqs. (4) and (6) are equivalent, and this justifies our interpretation of our experiments. Furthermore, the $1/R$ behavior shown in Fig. 1 (inset) not only implies that the living cell can be treated as a continuum, but also requires that the random force $f_i(\mathbf{x}, t)$ arises from a stress tensor of the form given in Eq. (3).

Last, we propose a microscopic picture of motor activities and derive a fluctuating stress tensor. Since motors are small but finite objects, their activities disturb the ambient cytoplasm in the form of a point dipole [20]. Since there is no net external force inside a stationary cell, by Newton's third law, the force exerted on the cytoplasm by a motor must be equal and opposite to that of the cytoplasm on that motor. Thus, the part of the stress tensor arising from deviations $\delta c_a(\mathbf{x}, t)$ of the coarse-grained activity density of motors from its average c_a is $s_{ij}(\mathbf{x}, t) = \Gamma(\hat{n}_i\hat{n}_j - \frac{1}{3}\delta_{ij})\delta c_a(\mathbf{x}, t)$, where $\hat{\mathbf{n}}$ is the direction of the point dipole and Γ is the energy scale. Since there is no preferred direction, we can average over all angles to obtain

$$\langle s_{ij}(\mathbf{x}, \omega)s_{kl}(\mathbf{x}', -\omega)\rangle = \frac{\Gamma^2}{15}\left[\delta_{ik}\delta_{jl} + \delta_{il}\delta_{jk} - \frac{2}{3}\delta_{ij}\delta_{kl}\right] \times\langle\delta c_a(\mathbf{x}, \omega)\delta c_a(\mathbf{x}', -\omega)\rangle, \quad (7)$$

which has exactly the same form of Eq. (3) if the fluctuations of motor activity is delta correlated in space. Furthermore, we can estimate the power associated with the stress fluctuations by computing the power dissipated per tracer: $\langle P\rangle = \int\frac{d\omega}{2\pi}\omega\mu''(\omega)\Delta(\omega)/|\mu(\omega)|^2 \sim 10^{-16}$ W. Estimating $\sim 10^3$ tracers per cell, the power to drive one cells' fluctuations is of the order of 10^{-13} W, which, as 1% of typical cell metabolism, is not unreasonable.

In conclusion, the interpretability of two-point microrheology in complex media, including cells, serves to clarify an otherwise confusing set of biophysical observations, supporting efforts to model cells as three-dimensional continua rather than cortical shells and suggesting that the cytoskeleton is a highly dynamic, actively stressed network. Future work to extend the temporal range and statistical power of such measurements should enable mapping and nontrivial spectroscopy of intracellular rheology and stress. Finally, such techniques may prove fruitful in other systems with nonthermal fluctuations, such as granular and jamming media.

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